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Signature: Gary K Fabian Gary R. Fabian Date: 1 June 2009

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE	
In Re Application of: SHEN,Y., et al.	Confirmation No.: 8135
Serial No.: 10/669,768	Art Unit: 1633
Filing Date: 24 September 2003	Examiner: Marvich, M.
Title: ADENOVIRUS E1B-55K SINGLE AMINO ACID MUTANTS AND METHODS OF USE	

REPLY BRIEF UNDER 37 C.F.R. § 41.41(a)(1)

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Dear Sir:

Introductory Remarks

This is in response to the Examiner's Answer, mailed 1 April 2009. Per M.P.E.P. §1208 (Eighth Edition) this Reply Brief contains the following:

(A) Identification page setting forth the Appellants' name(s), the application number, the filing date of the application, the title of the invention, the name of the examiner, the art unit of the examiner and the title of the paper (i.e., Reply Brief);

(B) Status of claims page(s);

(C) Grounds of rejection to be reviewed on appeal page(s); and

(D) Argument page(s).

Status of the Claims

Claims 11-13, 24-28, 33, and 35-40 are pending. Claims 11, 12, 24, 28, 33, 39 and 40 are rejected.

Claims 13, 25-27 and 35-38 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. (Office action, mailed 15 January 2008, page 8.)

Claims 1-10, 14-23, 29-32, 34, and 41-47 are canceled.

The rejection of claims 11, 12, 24, 28, 33, 39 and 40 is appealed herein.

Grounds Of Rejection To Be Reviewed On Appeal

Sole Issue

In the final Office action, dated 15 January 2008, the Examiner rejected claims 11, 12, 24, 28, 33, 39 and 40 under 35 U.S.C. §112, first paragraph, asserting (i) that the specification, while being enabling for treatment of cancer characterized by p53 loss or deficiency by direct administration Onyx 051 and 053 (comprises a single amino acid substitution in amino acid 240 or 260), does not reasonably provide enablement for any other embodiment, and (ii) that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. (Office action, mailed 15 January 2008, page 2.)

Argument

This Reply Brief is filed in view of section (10) of the Examiner's Answer, mailed 1 April 2009.

As part of the Examiner's argument regarding the asserted scope rejection, the Examiner asserts that "[t]he specification teaches the difficult nature of achieving such precise goals" (Examiner's Answer, page 8). The precise goals referred to by the Examiner appear to be the limitations of pending independent claims 11 and 33 that recombinant adenoviruses, used in the methods of the present invention, comprise (i) a single amino acid substitution mutation in the E1B-55K gene, the single amino acid substitution mutation reducing the ability of the mutated E1B-55K protein to bind to the tumor suppressor p53 when compared to the ability of wild-type E1B-55K protein to bind to the tumor suppressor p53, and (ii) the further property of retaining late viral function. The Examiner goes on to quote the specification as saying: "Thus far, all efforts to separate the p53 binding/inactivation and the late functions of the protein have been unsuccessful" (Examiner's Answer, page 9, emphasis by the Examiner). The Examiner seems to be attempting to use Appellants' description of the state of the prior art to negate Appellants' inventive contributions.

Prior to the teachings of the present specification, the ability to separate the E1B-55K functions of binding to p53 and retaining late viral function was a problem with no solution. However, one of Appellants' inventive contributions, as disclosed in the present application, provides a technical solution to this problem. The present specification clearly teaches one of ordinary skill in the art how to make recombinant adenovirus with reduced ability of E1B-55K protein to bind to the tumor suppressor p53 (when compared to the ability of wild-type E1B-55K protein to bind to the tumor suppressor p53) and retention of late viral function. *See* Appellants' Appeal Brief, pages 14-17.

The Examiner asserts that enablement of Appellants' claims requires undue experimentation because Appellants identified 2 out of 26 recombinant adenoviruses having the claimed characteristics. However, the Examiner has presented absolutely no evidence to support that identification of 2 recombinant adenoviruses, having the claimed characteristics, out of 26 screened adenoviruses imposes a burden of undue experimentation on one of ordinary skill in the art, particularly in the arts of molecular biology and medicine wherein the level of ordinary skill is quite high. Appellants, on the other hand, have shown one of ordinary skill in the art how to make and use recombinant adenoviruses having the claimed characteristics of the present invention (*see* Appeal

Brief, pages 14-17) and have presented arguments and evidence to support that identification of 2/26 recombinant adenoviruses having the claimed characteristics does NOT impose a burden of undue experimentation on one of ordinary skill in the art (*see* Appeal Brief, pages 20-24).

Regarding use of the recombinant adenoviruses of the present invention in the claimed methods of treating cancer, Appellants have consistently compared important phenotypes of ONYX-015 to the replication-selective recombinant adenoviruses of the present invention. Kirn, et al., (of record in the present application) discuss the use of adenovirus mutant *dl*1520 (ONYX-015) in clinical trials for the treatment of a number of cancer types. Appellants demonstrated that the recombinant adenoviruses of the present invention (i) showed substantially reduced binding of p53 (as does ONYX-015; *see* specification, Example 2, pages 19-22), (ii) showed protein synthesis profiles more similar to wild-type than to ONYX-015 which is an advantage because generally higher levels of adenoviral replication correspond to increased cytotoxicity in target cells (*see* specification, Example 3, pages 22-23), and, consistent with the previous observation, (iii) tumor cell specific cytolytic activity of the recombinant viruses of the present invention was higher than ONYX-015 (*see* specification, Example 4, page 23). Thus, it is clear from the data presented by Appellants that the recombinant adenoviruses of the present invention provide at least similar if not superior anti-cancer properties relative to ONYX-015, which has been demonstrated in clinical trials to be useful for the treatment of cancers. *See* Appeal Brief, pages 12-14.

The Examiner, however, has presented no evidence to support the assertion that use of the recombinant adenoviruses of the present invention in the claimed methods of treating a cancer is "unpredictable." As discussed in Appellants' Appeal Brief, the Examiner's assertions are contradicted by the teachings of the specification and the teachings of Kirn, et al.

Conclusion

In light of the foregoing, Appellants' Appeal Brief, the teachings of the specification, and the high level of skill of one of ordinary skill in the art, Appellants respectfully request the Board to reverse the rejection by the Examiner in this Application.

Respectfully submitted,

Date: 1 June 2009 By: Gary R Fabian

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